IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Toth et al.	Examiner:	Schlientz, N. W.
Application No.:	10/800,291	Group Art Unit:	1616
Filed:	March 12, 2004	Docket No.:	14669.0064USU1
Title:	STABLE PHARMACEUTICAL COMPOSITIONS OF DESLORATADINE		

DECLARATION UNDER 37 CFR 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

Now comes Declarant, Zoltán Gábor Tóth, Ph.D. who declares that:

1. All statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true.

2. I am a named co-inventor of the above-identified application.

3. I am employed by TEVA Gyogyszergyar Zartkoruen Mukodo Reszvenytarsasag, the named assignee of the above-identified application.

4. I understand the claimed subject matter of the above-identified application.

5. I understand the subject matter disclosed in each of the following references: Villani (U.S. Patent No. 4,659,716), Schumacher '855 (EP 0 208 855), Piwinski (WO 92/002293), and Schumacher (U.S. Patent No. 6,506,767).

6. I understand that the claims of the above-identified application have been rejected as being inherently anticipated by each one of Villani, Schumacher '855, and Piwinski (WO 92/002293).

7. The following experiments were performed under my supervision and control.

8. Under a vacuum using a jacket temperature of 50°C, 200 ml toluene solution of desloratadine was concentrated to approximately 150 ml of volume where precipitation was observed and a slurry was formed. The slurry was heated (80°C) to obtain a hot solution. The hot solution was cooled to 20°C for one hour. The

crystallized material was filtered off and dried in vacuum at room temperature. The sample presented a mixture of form 1 (9%) and form 2 (91%) by XRD.

9. Using a rotary-evaporator and a 50°C water bath, 100 ml toluene solution of desloratadine was concentrated by about 37% to obtain a slurry. The slurry was heated (100°C) to obtain a hot solution. The hot solution was cooled to room temperature. The precipitated material was filtered and dried in vacuum. The sample presented a form 2 (100%) by XRD.

10. Using a rotary-evaporator and a 50°C water bath, 100 ml toluene solution of desloratadine was concentrated by about ~ 64% to obtain a slurry. The slurry was heated (100°C) to obtain a hot solution. The hot solution was cooled to room temperature. The precipitated material was filtered off and dried in vacuum at room temperature. The sample presented form 2 (100%) by XRD.

11. Loratadine (6 g) was suspended in 70 % ethanol (30 ml) and 12 g NaOH was added. This slurry was heated at reflux temperature and stirred for 3 hours and a new portion of 70% ethanol (30 ml) was added to the reaction mixture, heating and stirring was continuous for additional 3 hours. After 17 hours of reaction time, the reaction mixture was cooled (50°C) and the solution was concentrated by approximately one-half the volume. Crushed ice (~100 ml) was added and the pH adjusted to about 6 with acetic acid (19 ml). The solution was extracted with chloroform 8 times (50 ml and 7 times 25 ml). The combined organic extract was concentrated to a minimual volume and addition of n-hexane (75 ml) resultant in precipitation. The solid material was filtered off and dried in vacuum at room temperature. The obtained product was 4.6 g of Desloratadine acetate.

12. Desloratadine acetate (4.52 g) in water (15 ml) and in 5% K_2CO_3 solution (7 ml) was stirred at room temperature. The solution was extracted with chloroform 6 times (3x25 ml and 3x15 ml). The combined organic extract was washed with water (30 ml) and was dried over Na_2SO_4 (10 g). The dried organic solution was concentrated to dryness and a brown oil was obtained. The brown oil was triturated with n-hexane to obtain a solid material. The solid material was filtered off and dried in vacuum at room temperature. The obtained product was 1.8 g of Desloratadine. The sample presented polymorphic form 2 by XRD.

13. Loratadine (6 g) was suspended in 70 % ethanol (30 ml) and 12 g NaOH was added. This slurry was heated at reflux temperature and stirred for 2 hours and a new portion of 70% ethanol (30 ml) was added to the reaction mixture, heating and stirring was continuous for additional 3 hours. After 5 hours of reaction time the reaction mixture was cooled (50°C) and concentrated by approximately one-half the volume. Crushed ice (100 ml) was added and the pH adjusted to about 6 with acetic acid (17 ml). The solution was extracted with chloroform 6 times (40 ml and 5 times 25 ml). The combined organic extract was concentrated to a minimal volume and the material was precipitated with n-hexane (75 ml). The solid material was filtered off and dried in

vacuum at room temperature. The obtained product was 4.53 g of Desloratadine acetate.

14. Desloratadine acetate (4.2 g) in water (30 ml) and in 5% K_2CO_3 solution (26 ml) was stirred at room temperature where an oily material appeared. The solution was extracted with chloroform 4 times (50 ml and 3 times 25 ml). The combined organic extract was washed with water (25 ml) and concentrated to a minimal volume, where a brown oil was obtained. The material was precipitated with n-hexane (25 ml). The solid material was filtered off and dried in vacuum at room temperature. The obtained product was 3.06 g of Desloratadine. The sample presented a mixture of form 1 (25%) and form 2 (75%) by XRD.

15. Desloratadine (3 g) was dissolved in chloroform (30 ml) at room temperature. The pink-colored solution was decolorized by using charcoal (0.15 g). After filtration of charcoal the solution was concentrated to dryness using a rotary-evaporator at 40°C. The residue oil was sucked under vacuum until the oil was solidified. The solid material was dried. This sample contained form 2 with a trace of form 1.

16. Desloratadine (3 g) was dissolved in chloroform (30 ml) at room temperature. The pink-colored solution was decolorized by using charcoal (0.15 g). After filtration of charcoal the solution was concentrated to dryness by using a rotary-evaporator at 40°C. The residue oil was triturated with n-hexane (7.5 ml). The solid material was filtered off and was dried in vacuum. The sample of polymorphic forms was checked by XRD. This sample was presented form 2 with trace of form 1.

17. Desloratadine (9 g) was suspended in n-hexane (45 ml) at reflux temperature for 24 hours. The slurry was cooled down to room temperature and solid material was filtered off and dried. The sample presented a mixture of form 1 and form 2 by XRD.

18. Desloratadine (3 g) was suspended in n-hexane (20 ml) and stirred at reflux temperature for 24 hours. The slurry was cooled down to room temperature and solid material was filtered off and dried in vacuum at room temperature. 2.87 g of desloratadine was obtained and this sample was presented form 1 by XRD. The polymorphic form was not changed.

19. Desloratadine (3 g) was suspended in n-hexane (20 ml) and the slurry was inserted to a sonicator for using of ultrasonic radiation for 2.5 hours. During the use of ultrasonic radiation the temperature was 38°C. The slurry was cooled down to room temperature and solid material was filtered off and dried in vacuum at room temperature. 2.6 g of desloratadine was obtained and this sample was presented form 1 by XRD. The polymorphic form was not changed.

20. Desloratadine (3 g) was suspended in n-heptane (20 ml) and the slurry was inserted to a sonicator for using of ultrasonic radiation for 2.5 hours. During the use of ultrasonic radiation the temperature was 44°C. The slurry was cooled down to room temperature and solid material was filtered off and dried in vacuum at room temperature. 2.5 g of

desloratadine was obtained and this sample was presented form I by XRD. The polymorphic form was not changed.

21. Desloratadine (3 g) was suspended in n-hexane (20 ml) and stirred at reflux temperature for 24 hours. The slurry was cooled down to room temperature and solid material was filtered off and dried in vacuum at room temperature. 2.78 g of desloratadine was obtained and this sample was presented form 1 by XRD. The polymorphic form was not changed.

22. To a vessel containing desloratadine (0.1 g) was added 10 ml of n-hexane (in 0.1 ml portions) at room temperature. The amount of desloratadine did not dissolve in 10 ml n-hexane and this sample was not checked by XRD.

23. To a vessel containing desloratadine (0.1 g) was added 20 ml of n-hexane (in 0.1 ml portions) at 45°C. The amount of desloratadine did not dissolve in 20 ml n-hexane and this sample was not checked by XRD.

24. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Zoltán Gábor Tóth

Zoltán Gábor Tóth, Ph.D

09/06/2005

Date